CHANNEL, 1998 a

DEPARTMENT OF THE AIR FORCE
AIR FORCE RESEARCH LABORATORY
WRIGHT-PATTERSON AIR FORCE BASE OHIO 45433

27 OCT 98

MEMORANDUM FOR EPA
NCEA (MD-52)
RTP, NC 27711
ATTN: Annie Jarabek

FROM: AFRL/HEST
2856 G Street
Wright-Patterson AFB OH 45344-7400

SUBJECT: Consultative Letter, AFRL-HE-WP-CL-1998-0026, Histopathology Report for Thyroids from a Fourteen-Day Oral Dosing Toxicity Study of Ammonium Perchlorate

1. **Design:**

Groups of six male and six female Sprague-Dawley rats were dosed with AP in drinking water at concentrations of 0 (control), 1.25, 5.0, 12.5, 25, 50, 125, or 250 mg/L (Caldwell, et al. 1995). The actual dose of AP administered to each animal was calculated by multiplying the concentration of AP administered in the drinking water by each animal's average water consumption over the 14-day period and dividing this number by each animal's average body weight over the 14-day period. Animals were sacrificed after fourteen days. Thyroids were collected and prepared for histopathological analysis.

2. **Histopathology:**

Histopathological analysis was performed and reported by Eggers (1996) and included as Attachment 1. Individual animal histology data is included as Attachment 2.

3. **Results and Comments:**

Incidence of follicular epithelial cell hypertrophy and decrease in follicular lumen size is summarized in Table 1. Changes in epithelial cells and follicular lumen size were present in all thyroids examined starting with the 25 mg/kg group. Severity of follicular epithelial cell hypertrophy and and decrease in follicular lumen size is summarized in

Table 2. The change in hypertrophy was significantly different from control at a lower dose of ammonium perchlorate (5 mg/kg) than the change in lumen area (25 mg/kg). The scoring parameters for severity are shown in Table 3. Statistical analysis reported by Eggers (1996) in his histopathology report is the combined analysis of male and female rats and documentation is not on file. It is recommended that the statistics be performed again and the documentation included in the final report.

TABLE 1. INCIDENCE OF THYROID FOLLICULAR CELL HYPERTROPHY AND DECREASE IN FOLLICULAR LUMEN SIZE IN MALE AND FEMALE RATS EXPOSED TO AMMONIUM PERCHLORATE IN DRINKING WATER FOR 14 DAYS

A. INCIDENCE OF THYROID FOLLICULAR CELL HYPERTROPHY

			MALE				
CONTROL	1.25	5.0	12.5	25	50	125	250
2	5	5	5	6	6	6	6
			FEMALE				
CONTROL	1.25	5.0	12.5	25	50	125	250
2	1[a]	5	4	6	6	6	6

[a] n=5

B. INCIDENCE OF FOLLICULAR LUMEN SIZE DECREASE

			MALE				
CONTROL	1.25	5.0	12.5	25	50	125	250
3	4	5	5	6	6	6	6
			FEMALE				
CONTROL	1.25	5.0	12.5	25	50	125	250
4	2[a]	6	5	6	6	6	6

[a] n=5

TABLE 2. SEVERITY OF THYROID FOLLICULAR CELL HYPERTROPHY AND DECREASE IN FOLLICULAR LUMEN SIZE IN MALE AND FEMALE RATS EXPOSED TO AMMONIUM PERCHLORATE IN DRINKING WATER FOR 14 DAYS

MEAN
± STANDARD DEVIATION

A. SEVERITY OF THYROID FOLLICULAR CELL HYPERTROPHY

			MALE				
CONTROL	1.25	5.0	12.5	25	50	125	250
0.67	1.67	1.83	2.0	2.67	3.0	3.67	4.0
0.94	0.75	0.9	1.15	0.94	1.0	0.75	0.0

			FEMALE				
CONTROL	1.25	5.0	12.5	25	50	125	250
0.67	0.40[a]	1.67	1.33	2.67	2.67	3.33	4.00
0.94	0.80	0.75	0.94	0.94	0.94	0.94	0.00

[a] n=5

B. SEVERITY OF FOLLICULAR LUMEN SIZE DECREASE

			MALE				
CONTROL	1.25	5.0	12.5	25	50	125	250
0.50	0.67	0.83	1.50	1.67	3.33	4.33	4.00
0.50	0.47	0.37	1.12	0.94	0.75	0.94	1.00

			FEMALE				
CONTROL	1.25	5.0	12.5	25	50	125	250
0.67	0.40[a]	1.00	0.83	1.67	1.67	3.00	4.00
0.47	0.49	0.00	0.37	0.94	0.94	1.26	1.00

[a] n=5

Table 3. Scoring parameters for severity of hypertrophy and decrease in follicular lumen size.

Normal	0
Slight	1
Mild	2
Moderate	3
Marked	4
Severe	5

4. **Reference:**

Caldwell, D.J., Kinkead, E.R., Narayanan, L., King, J.H. and Mattie, D.R. Results of a Fourteen Day Oral-Dosing Toxicity Study of Ammonium Perchlorate. 1995 JANNAF Safety and Environmental Protection Subcommittee. CPIA Publication 634, Vol. 1:179-184, Tampa, FL, 4-8 Dec 1995.

Eggers, J. 1996. Toxicity evaluation of ammonium perchlorate administered in the drinking water of Sprague-Dawley rats. Study A10. A Narrative Pathology Report – Pilot Study.

5. **Scientific POC:**

This report was prepared by David R. Mattie, PHD, in collaboration with Dr Jeffrey Eggers, pathologist. Dr Mattie can be reached at AFRL/HEST, Wright-Patterson AFB, OH (937) 255-5150, ext 3110, E-Mail: mattied@falcon.al.wpafb.af.mil

Stephen R. Channel, Maj., USAF, BSC
Chief, Operational Toxicology Branch
Human Effectiveness Directorate

ATTACHMENT 1.

TOXICITY EVALUATION OF AMMONIUM PERCHLORATE ADMINISTERED IN THE DRINKING WATER OF SPRAGUE-DAWLEY RATS

Study number A10 — Study Director: D. Caldwell
Start date 25 July, 1995 — Study Pathologist: J. Eggers

NARRATIVE PATHOLOGY REPORT - PILOT STUDY

Gross observations:
At necropsy, all rats utilized in this study were in good general condition. Both edema and atrophy of the thyroid gland were diagnosed grossly in low numbers of animals from control and treatment groups, and these findings did not appear to be dose related. Thyroid enlargement was noted grossly in one high dose (250 mg/kg) female and in one mid dose (25 mg/kg) male animal.

Histopathology:
The thyroid gland was the only tissue examined histologically in this 14-day pilot study. Averages of both thyroid follicular lumen size and thyroid follicular epithelial hypertrophy were estimated using a standard microscope ocular grid as a reference for measurement. The incidence and average severity score for each finding are noted in table 1. There was no statistical difference between males and females in the incidence or dose response for either finding.

Follicular lumen size (colloid area): There was a dose-related decrease in follicular lumen size starting at the 5 mg/kg dose progressing to the 250 mg/kg (high) dose group. Follicular lumens in the 25, 50, 125, and 250 mg/kg dose groups were significantly ($p<0.01$) decreased in area compared to controls (Table 2). The progressive decrease in lumen size was also statistically significant ($p<0.01$) between different dosage groups as follows: control through 12.5 mg/kg > 2.5 mg/kg > 50 mg/kg > 125 and 250 mg/kg.

Follicular epithelial cell hypertrophy: A significant ($p<0.01$) dose-related increase in severity of follicular cell hypertrophy was observed in the all except the lowest (1.25 mg/kg) dose group as compared to controls. The progressive increase in follicular cell hypertrophy was also statistically significant ($p<0.01$) between different dosage groups as follows: Control and 1.25 mg/kg < 5 and 12.5 mg/kg < 25 and 50 mg/kg < 125 and 250 mg/kg (Table 2).

Morphometry: Computerized morphometric image analysis of follicular lumen size was performed on 5 dose groups (Controls, 1.25 mg/kg, 12.5 mg/kg, 50 mg/kg, 250 mg/kg). A statistically significant ($p<0.01$) decrease in lumen size was evident in 12.5, 50, and 250 mg/kg dose groups in male rats and in 50 and 250 mg/kg dose groups in female rats compared to controls.

Discussion:

Although there was no statistical difference in severity between males and females for the histomorphologic changes, in general, male rats appeared more sensitive to perchlorate effects on the thyroid at most dose levels. This was also true of thyroid follicular lumen area as measured by morphometry.

The thyroid gland is considered a target organ of perchlorate toxicity. The pathogenesis of perchlorates effect on the thyroid is thought to be through inhibition of I uptake by the gland resulting in decreased levels of circulating T3 and T4 hormones. The morphologic changes in the thyroid follicles observed in this study are most likely due to a change in thyroid follicular epithelium function in response to increasing TSH levels secondary to decreasing T3 and T4 hormones. Therefore, the best parameter to determine a no observed adverse effect level (NOEL) for perchlorate in relation to rat thyroid gland function may be the maximum dose that does not significantly increase TSH levels in these animals.

Jeffrey S. Eggers
MAJ, VC, USA
Chief, AMRU

3 Feb 96

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NOTE: PRINTED FOR : JEFF EGGERS (A)

Table 1

Save

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PPPP    AAA   TTTTT  H   H  TTTTT   OOO   X   X
P   P  A   A    T    H   H    T    O   O  X   X
P   P  A   A    T    H   H    T    O   O   X X
PPPP   A   A    T    HHHHH    T    O   O    X
P      AAAAA    T    H   H    T    O   O   X X
P      A   A    T    H   H    T    O   O  X   X
P      A   A    T    H   H    T     OOO   X   X
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FFFFFFFFFF    OOOOOO    RRRRRRRR      000000      000000      333333
FFFFFFFFFF    OOOOOO    RRRRRRRR      000000      000000      333333
FF          OO      OO  RR      RR  00      00  00      00  33      33
FF          OO      OO  RR      RR  00      00  00      00  33      33
FF          OO      OO  RR      RR  00    0000  00    0000        33
FF          OO      OO  RR      RR  00    0000  00    0000        33
FFFFFFFF    OO      OO  RRRRRRRR    00  00  00  00  00  00      33
FFFFFFFF    OO      OO  RRRRRRRR    00  00  00  00  00  00      33
FF          OO      OO  RR  RR      0000    00  0000    00        33
FF          OO      OO  RR  RR      0000    00  0000    00        33
FF          OO      OO  RR    RR    00      00  00      00  33    33
FF          OO      OO  RR    RR    00      00  00      00  33    33
FF            OOOOOO    RR      RR    000000      000000      333333
FF            OOOOOO    RR      RR    000000      000000      333333

                DDDDDDDD      AAAAAA    TTTTTTTTTT      ;;;;    5555555555
                DDDDDDDD      AAAAAA    TTTTTTTTTT      ;;;;    5555555555
                DD      DD  AA      AA      TT          ;;;;    55
                DD      DD  AA      AA      TT          ;;;;    55
                DD      DD  AA      AA      TT                  555555
                DD      DD  AA      AA      TT                  555555
                DD      DD  AA      AA      TT          ;;;;          55
                DD      DD  AA      AA      TT          ;;;;          55
                DD      DD  AAAAAAAAAA      TT          ;;;;            55
                DD      DD  AAAAAAAAAA      TT          ;;;;            55
....            DD      DD  AA      AA      TT            ;;    55      55
....            DD      DD  AA      AA      TT            ;;    55      55
....            DDDDDDDD    AA      AA      TT          ;;        555555
....            DDDDDDDD    AA      AA      TT          ;;        555555
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Incidence Summary of Microscopic Observations
Study number: aprf1
All Diagnoses
Study start date: 25-Jul-95

ORAL UPTAKE/REPEATED DOSE, GAVAGE

Notes: Animals = all dead animals
Controls from group(s): 1
Dosing units: (mg/kg)

Tissues With Diagnoses	Animal sex	-- Animals Affected --							
		-- Males --							
	Group dosage level:	Ctls	1.2500	5.0000	12.500	25.000	50.000	******	******
	No. in group:	6	6	6	6	6	6	6	6
THYROID	Number examined:	6	6	6	6	6	6	6	6
follicular cell hypertrophy/hyperplasia		2	5	5	5	6	6	-6	-6
follicular lumen size (decreasing colloid area)	1	3	4	5	5	6	-6	-6	-6

Note: Entries flagged with a - (minus) are significantly different from control at the 0.05 level using the Kolmogorov-Smirnov two tailed test.

Notes: Animals = all dead animals
Controls from group(s): 1
Dosing units: (mg/kg)

Tissues With Diagnoses	Animal sex:	-- Animals Affected -- Females --							
	Group dosage level:	Ctls	1.2500	5.0000	12.500	25.000	50.000	******	******
	No. in group:	6	6	6	6	6	6	6	6
THYROID ..... Number examined:		6	5	6	6	6	6	6	6
follicular cell hypertrophy/hyperplasia		2	1	5	4	6	6	6	-6
follicular lumen size (decreasing colloid area)		1 4	2	6	5	6	6	-6	-6

Note: Entries flagged with a - (minus) are significantly different from control at the 0.05 level using the Kolmogorov-Smirnov two tailed test.

Summary Table of Microscopic Observations With Average Severity Grade
Study number: aprf1
Nonneoplastic Graded Diagnoses
Study start date: 25-Jul-95

ORAL UPTAKE/REPEATED DOSE, GAVAGE

Notes: Animals = all dead animals
Controls from group(s): 1
Dosing units: (mg/kg)

Tissues With Diagnoses		-- Animals Affected -- Males --							
Animal sex:									
Group dosage level:		Ctls	1.2500	5.0000	12.500	25.000	50.000	******	******
No. in group:		6	6	6	6	6	6	6	6
THYROID	Number examined:	6	6	6	6	6	6	6	6
follicular cell hypertrophy/hyperplasia		2	5	5	5	6	6	6	6
	Average severity:	0.7	1.7	2.0	2.0	2.7	3.0	3.7	4.0
follicular lumen size (decreasing colloid area)1		3	4	5	5	6	6	6	6
	Average severity:	0.5	0.7	0.8	1.5	1.7	3.3	4.3	4.0

Summary Table of Microscopic Observations With Average Severity Grade
Study number: aprf1
Nonneoplastic Graded Diagnoses
Study start date: 25-Jul-95

ORAL UPTAKE/REPEATED DOSE, GAVAGE

Notes: Animals = all dead animals
Controls from group(s): 1
Dosing units: (mg/kg)

Tissues With Diagnoses		-- Animals Affected -- Females --							
	Animal sex:								
	Group dosage level:	Ctls	1.2500	5.0000	12.500	25.000	50.000	******	******
	No. in group:	6	6	6	6	6	6	6	6
THYROID	Number examined:	6	5	6	6	6	6	6	6
follicular cell hypertrophy/hyperplasia		2	1	5	4	6	6	6	6
	Average severity:	0.7	0.4	1.7	1.3	2.7	2.7	3.3	4.0
follicular lumen size (decreasing colloid area)	1	4	2	6	5	6	6	6	6
	Average severity:	0.7	0.4	1.0	0.8	1.7	1.7	3.0	4.0

Animal: 22 Sex: Male Group: 8 Dose level: 250.000 (mg/kg)
Day of death: 15 Status: Final sacrifice Terminal body weight (kgs): 0.43

Tissue	Gross observations / Comments	Microscopic observations / Comments

Animal: 10 Sex: Male Group: 8 Dose level: 250.000 (mg/kg)
Day of death: 14 Status: Final sacrifice Terminal body weight (kgs): 0.59

Tissue	Gross observations / Comments	Microscopic observations / Comments

Animal: 23 Sex: Male Group: 8 Dose level: 250.000 (mg/kg)
Day of death: 15 Status: Final sacrifice Terminal body weight (kgs): 0.49

Tissue	Gross observations / Comments	Microscopic observations / Comments

Animal: 3 Sex: Male Group: 8 Dose level: 250.000 (mg/kg)
Day of death: 14 Status: Final sacrifice Terminal body weight (kgs): 0.55

Tissue	Gross observations / Comments	Microscopic observations / Comments
THYROID	ENLARGED/	follicular cell hypertrophy/hyperplasia, Marked. follicular lumen size (decreasing colloid area)1, Severe.

Animal: 37 Sex: Male Group: 8 Dose level: 250.000 (mg/kg)
Day of death: 15 Status: Final sacrifice Terminal body weight (kgs): 0.49

Tissue	Gross observations / Comments	Microscopic observations / Comments

Animal: 18 Sex: Male Group: 8 Dose level: 250.000 (mg/kg)
Day of death: 14 Status: Final sacrifice Terminal body weight (kgs): 0.54

Tissue	Gross observations / Comments	Microscopic observations / Comments
THYROID	EDEMA/	follicular cell hypertrophy/hyperplasia, Marked. follicular lumen size (decreasing colloid area)1, Moderate.

Animal Number	Sex	Group/ Subgroup	Date and Time Data was entered	Oper. #	Tissue	Special histological comment
55	F	2/1	10-Oct-95 10:53	88	THYROID	thyroid lost in processing
59	F	5/1	10-Oct-95 10:57	88	THYROID	ultimobranchial cyst
80	F	5/1	10-Oct-95 10:58	88	THYROID	ultimobranchial cyst

Table 2. Histo statistics

	Control	1.25	5	12.5	25	50	125	250	
1	0.67	1.09	1.83	1.67	2.67	2.83	3.50	4.00	hypertrophy / hyperplasia
2	0.58	0.55	0.92	1.19	1.67	2.50	3.67	4.00	lumen size

significant at $P = 0.01$

CD7

underlined means that the groups are the same

The sex of the animal did not affect the dose-response.

Study aprf1
Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 24 Sex: Male Group: 1 Dose level: 0.0000 (mg/kg)
Day of death: 14 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments

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GEN CONDITION . . . GOOD/ ,NGL - PP

The following tissues are examined/unremarkable microscopically: THYROID

Study aprf1

Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 39 Sex: Male Group: 1 Dose level: 0.0000 (mg/kg)

Day of death: 15 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments
GEN CONDITION . . .	GOOD/ ,ngl-jwn	

The following tissues are examined/unremarkable microscopically: THYROID

Study aprf1
Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 11 Sex: Male Group: 1 Dose level: 0.0000 (mg/kg)
Day of death: 14 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments
THYROID	EDEMA/ ,SLIGHT SWELLING AROUND THYROIDS - PP	follicular lumen size (decreasing colloid area)1, Slight.

Study aprf1
Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 15 Sex: Male Group: 1 Dose level: 0.0000 (mg/kg)
Day of death: 14 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments
THYROID	No gross observed on tissue.	follicular cell hypertrophy/hyperplasia, Mild. follicular lumen size (decreasing colloid area)1, Slight.
GEN CONDITION . . .	GOOD/ ,NGL - PP	

Study aprf1
Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 47 Sex: Male Group: 1 Dose level: 0.0000 (mg/kg)
Day of death: 15 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments
THYROID	No gross observed on tissue.	follicular cell hypertrophy/hyperplasia, Mild.
GEN CONDITION . . .	GOOD/ ,ngl-jwn	

Study aprf1

Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 44 Sex: Male Group: 1 Dose level: 0.0000 (mg/kg)

Day of death: 15 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments
THYROID	No gross observed on tissue.	follicular lumen size (decreasing colloid area)1, Slight.
GEN CONDITION . . .	GOOD/ ,ngl-jwn	

Study aprf1
Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 12 Sex: Male Group: 2 Dose level: 1.2500 (mg/kg)
Day of death: 14 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments
THYROID	No gross observed on tissue.	follicular lumen size (decreasing colloid area)1, Slight.
GEN CONDITION . . .	GOOD/ ,NGL - PP	

Study aprf1
Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 14 Sex: Male Group: 2 Dose level: 1.2500 (mg/kg)
Day of death: 14 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments
THYROID	EDEMA/ ,AROUND THYROIDS - PP	follicular cell hypertrophy/hyperplasia, Mild.

Study aprf1
Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 27 Sex: Male Group: 2 Dose level: 1.2500 (mg/kg)
Day of death: 15 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments
THYROID	No gross observed on tissue.	follicular cell hypertrophy/hyperplasia, Mild. follicular lumen size (decreasing colloid area)1, Slight.
GEN CONDITION . . .	GOOD/ ,NGL-JWN	

Study aprf1
Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 25 Sex: Male Group: 2 Dose level: 1.2500 (mg/kg)
Day of death: 15 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments
THYROID	No gross observed on tissue.	follicular cell hypertrophy/hyperplasia, Mild. follicular lumen size (decreasing colloid area)1, Slight.
GEN CONDITION . . .	GOOD/ ,ngl-jwn	

Study aprf1

Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 19 Sex: Male Group: 2 Dose level: 1.2500 (mg/kg)

Day of death: 15 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments
THYROID	No gross observed on tissue.	follicular cell hypertrophy/hyperplasia, Mild. follicular lumen size (decreasing colloid area)1, Slight.
GEN CONDITION . . .	GOOD/ ,ngl-jwn	

Study aprf1

Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 1 Sex: Male Group: 2 Dose level: 1.2500 (mg/kg)

Day of death: 14 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments
THYROID	atrophy/ ,LEFT IS ATROPHIED - PP	follicular cell hypertrophy/hyperplasia, Mild.

Study aprf1
Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 13 Sex: Male Group: 3 Dose level: 5.0000 (mg/kg)
Day of death: 14 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments
THYROID	EDEMA/ ,MILD SWELLING AROUND THYROIDS - PP	follicular cell hypertrophy/hyperplasia, Marked. follicular lumen size (decreasing colloid area)1, Slight.

Study aprf1
Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 9 Sex: Male Group: 3 Dose level: 5.0000 (mg/kg)
Day of death: 14 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments
THYROID	EDEMA/ ,SLIGHT AROUND THYROIDS - PP	follicular cell hypertrophy/hyperplasia, Mild. follicular lumen size (decreasing colloid area)1, Slight.

Study aprf1
Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 48 Sex: Male Group: 3 Dose level: 5.0000 (mg/kg)
Day of death: 15 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments
THYROID	No gross observed on tissue.	follicular cell hypertrophy/hyperplasia, Mild. follicular lumen size (decreasing colloid area)1, Slight.
GEN CONDITION . . .	GOOD/ ,ngl-jwn	

Study aprf1
Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 42 Sex: Male Group: 3 Dose level: 5.0000 (mg/kg)
Day of death: 15 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments
THYROID	No gross observed on tissue.	follicular cell hypertrophy/hyperplasia, Mild. follicular lumen size (decreasing colloid area)1, Slight.
GEN CONDITION . . .	GOOD/ ,ngl-jwn	

Study aprf1

Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 29 Sex: Male Group: 3 Dose level: 5.0000 (mg/kg)

Day of death: 15 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments
GEN CONDITION . . .	GOOD/ ,ngl-jwn	

The following tissues are examined/unremarkable microscopically: THYROID

Study aprf1
Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 21 Sex: Male Group: 3 Dose level: 5.0000 (mg/kg)
Day of death: 14 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments
THYROID	No gross observed on tissue.	follicular cell hypertrophy/hyperplasia, Mild. follicular lumen size (decreasing colloid area)1, Slight.
GEN CONDITION . . .	GOOD/ ,NGL - PP	

Study aprf1

Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 41 Sex: Male Group: 4 Dose level: 12.5000 (mg/kg)

Day of death: 15 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments
THYROID	No gross observed on tissue.	follicular cell hypertrophy/hyperplasia, Marked. follicular lumen size (decreasing colloid area)1, Moderate.
GEN CONDITION . . .	GOOD/ ,ngl-jwn	

Study aprf1
Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 17 Sex: Male Group: 4 Dose level: 12.5000 (mg/kg)
Day of death: 14 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments
THYROID	No gross observed on tissue.	follicular cell hypertrophy/hyperplasia, Mild. follicular lumen size (decreasing colloid area)1, Moderate.
GEN CONDITION . . .	GOOD/ ,NGL - PP	

Study aprf1
Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 38 Sex: Male Group: 4 Dose level: 12.5000 (mg/kg)
Day of death: 15 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments
THYROID	No gross observed on tissue.	follicular cell hypertrophy/hyperplasia, Mild.
GEN CONDITION . . .	GOOD/ ,ngl-jwn	

Study aprf1

Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 26 Sex: Male Group: 4 Dose level: 12.5000 (mg/kg)

Day of death: 14 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments
THYROID	EDEMA/ ,around and under thyroids -pp	follicular lumen size (decreasing colloid area)1, Slight.

Study aprf1
Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 20 Sex: Male Group: 4 Dose level: 12.5000 (mg/kg)
Day of death: 14 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments
THYROID	No gross observed on tissue.	follicular cell hypertrophy/hyperplasia, Mild. follicular lumen size (decreasing colloid area)1, Slight.
GEN CONDITION . . .	GOOD/ ,NGL - PP	

Study aprf1
Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 45 Sex: Male Group: 4 Dose level: 12.5000 (mg/kg)
Day of death: 15 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments
THYROID	No gross observed on tissue.	follicular cell hypertrophy/hyperplasia, Mild. follicular lumen size (decreasing colloid area)1, Slight.
GEN CONDITION . . .	GOOD/ ,NGL-JWN	

Study aprf1
Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 30 Sex: Male Group: 5 Dose level: 25.0000 (mg/kg)
Day of death: 15 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments
THYROID	No gross observed on tissue.	follicular cell hypertrophy/hyperplasia, Mild. follicular lumen size (decreasing colloid area)1, Slight.
GEN CONDITION . . .	GOOD/ ,ngl-jwn	

Study aprf1

Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 16 Sex: Male Group: 5 Dose level: 25.0000 (mg/kg)

Day of death: 14 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments
THYROID	atrophy/ ,LEFT SIDE - PP	follicular cell hypertrophy/hyperplasia, Marked. follicular lumen size (decreasing colloid area)1, Moderate.

Study aprf1

Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 7 Sex: Male Group: 5 Dose level: 25.0000 (mg/kg)

Day of death: 14 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments
THYROID	EDEMA/ ,SLIGHT AROUND THYROIDS - PP	follicular cell hypertrophy/hyperplasia, Marked. follicular lumen size (decreasing colloid area)1, Slight.

Study aprf1
Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 36 Sex: Male Group: 5 Dose level: 25.0000 (mg/kg)
Day of death: 15 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments
THYROID	No gross observed on tissue.	follicular cell hypertrophy/hyperplasia, Mild. follicular lumen size (decreasing colloid area)1, Slight.
GEN CONDITION . . .	GOOD/ ,ngl-jwn	

Study aprf1

Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 4 Sex: Male Group: 5 Dose level: 25.0000 (mg/kg)

Day of death: 14 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments
THYROID	atrophy/ ,SLIGHT AROUND THYROIDS - PP	follicular cell hypertrophy/hyperplasia, Mild.
	atrophy/ ,RIGHT SMALLER	follicular lumen size (decreasing colloid area)1, Moderate.

Study aprf1
Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 43 Sex: Male Group: 5 Dose level: 25.0000 (mg/kg)
Day of death: 15 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments
THYROID	No gross observed on tissue.	follicular cell hypertrophy/hyperplasia, Mild. follicular lumen size (decreasing colloid area)1, Slight.
GEN CONDITION . . .	GOOD/ ,NGL-JWN	

Study aprf1
Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 33 Sex: Male Group: 6 Dose level: 50.0000 (mg/kg)
Day of death: 14 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments
THYROID	atrophy/ ,left,slightly,edema around thyroid - PP	follicular cell hypertrophy/hyperplasia, Mild. follicular lumen size (decreasing colloid area)1, Moderate.

Study aprf1
Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 46 Sex: Male Group: 6 Dose level: 50.0000 (mg/kg)
Day of death: 15 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments
THYROID	No gross observed on tissue.	follicular cell hypertrophy/hyperplasia, Marked. follicular lumen size (decreasing colloid area)1, Moderate.
GEN CONDITION . . .	GOOD/ ,ngl-jwn	

Study aprf1

Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 8 Sex: Male Group: 6 Dose level: 50.0000 (mg/kg)

Day of death: 14 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments
THYROID	No gross observed on tissue.	follicular cell hypertrophy/hyperplasia, Mild. follicular lumen size (decreasing colloid area)1, Moderate.
GEN CONDITION . . .	GOOD/ ,NGL - PP	

Study aprf1

Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 6 Sex: Male Group: 6 Dose leve.: 50.0000 (mg/kg)

Day of death: 14 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments
THYROID	atrophy/ ,LEFT SIDE - PP	follicular cell hypertrophy/hyperplasia, Mild. follicular lumen size (decreasing colloid area)1, Moderate.

Study aprf1
Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 34 Sex: Male Group: 6 Dose level: 50.0000 (mg/kg)
Day of death: 15 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments
THYROID	No gross observed on tissue.	follicular cell hypertrophy/hyperplasia, Marked. follicular lumen size (decreasing colloid area)1, Severe.
GEN CONDITION . . .	GOOD/ ,ngl-jwn	

Study aprf1
Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 40 Sex: Male Group: 6 Dose level: 50.0000 (mg/kg)
Day of death: 15 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments
THYROID	No gross observed on tissue.	follicular cell hypertrophy/hyperplasia, Marked. follicular lumen size (decreasing colloid area)1, Moderate.
GEN CONDITION . . .	GOOD/ ,ngl-jwn	

Study aprf1

Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 28 Sex: Male Group: 7 Dose level: 125.000 (mg/kg)

Day of death: 14 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments
THYROID	No gross observed on tissue.	follicular cell hypertrophy/hyperplasia, Marked. follicular lumen size (decreasing colloid area)1, Severe.
GEN CONDITION . . .	GOOD/ ,NGL - PP	

Study aprf1
Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 2 Sex: Male Group: 7 Dose level: 125.000 (mg/kg)
Day of death: 14 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments
THYROID	No gross observed on tissue.	follicular cell hypertrophy/hyperplasia, Mild. follicular lumen size (decreasing colloid area)1, Moderate.
GEN CONDITION . . .	GOOD/ ,NGL - PP	

Study aprf1
Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 32 Sex: Male Group: 7 Dose level: 125.000 (mg/kg)
Day of death: 15 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments
THYROID	No gross observed on tissue.	follicular cell hypertrophy/hyperplasia, Marked. follicular lumen size (decreasing colloid area)1, Moderate.
GEN CONDITION . . .	GOOD/ ,ngl-jwn	

Study aprf1
Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 35 Sex: Male Group: 7 Dose level: 125.000 (mg/kg)
Day of death: 15 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments
THYROID	No gross observed on tissue.	follicular cell hypertrophy/hyperplasia, Marked. follicular lumen size (decreasing colloid area)1, Severe.
GEN CONDITION . . .	GOOD/ ,ngl-jwn	

Study aprf1
Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 31 Sex: Male Group: 7 Dose level: 125.000 (mg/kg)
Day of death: 15 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments
THYROID	No gross observed on tissue.	follicular cell hypertrophy/hyperplasia, Marked. follicular lumen size (decreasing colloid area)1, Severe.
GEN CONDITION . . .	GOOD/ ,ngl-jwn	

Study aprf1
Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 5 Sex: Male Group: 7 Dose level: 125.000 (mg/kg)
Day of death: 14 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments
THYROID	atrophy/ ,LEFT - PP	follicular cell hypertrophy/hyperplasia, Marked. follicular lumen size (decreasing colloid area)1, Severe.

Study aprf1
Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 22 Sex: Male Group: 8 Dose level: 250.000 (mg/kg)
Day of death: 15 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments
THYROID	No gross observed on tissue.	follicular cell hypertrophy/hyperplasia, Marked. follicular lumen size (decreasing colloid area)1, Severe.
GEN CONDITION . . .	GOOD/ ,ngl-jwn	

Study aprf1

Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 10 Sex: Male Group: 8 Dose level: 250.000 (mg/kg)

Day of death: 14 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments
THYROID	No gross observed on tissue.	follicular cell hypertrophy/hyperplasia, Marked. follicular lumen size (decreasing colloid area)1, Moderate.
GEN CONDITION . . .	GOOD/ ,NGL - PP	

Study aprf1
Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 23 Sex: Male Group: 8 Dose level: 250.000 (mg/kg)
Day of death: 15 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments
THYROID	No gross observed on tissue.	follicular cell hypertrophy/hyperplasia, Marked. follicular lumen size (decreasing colloid area)1, Moderate.
GEN CONDITION . . .	GOOD/ ,NGL-JWN	

Study aprf1

Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 3 Sex: Male Group: 8 Dose level: 250.000 (mg/kg)

Day of death: 14 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments
THYROID	ENLARGED/ ,RIGHT ENLARGED 2X AND DARK BROWN - PP	follicular cell hypertrophy/hyperplasia, Marked. follicular lumen size (decreasing colloid area)1, Severe.

Study aprf1

Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 37 Sex: Male Group: 8 Dose level: 250.000 (mg/kg)

Day of death: 15 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments
THYROID	No gross observed on tissue.	follicular cell hypertrophy/hyperplasia, Marked. follicular lumen size (decreasing colloid area)1, Severe.
GEN CONDITION . . .	GOOD/ ,NGL-JWN	

Study aprf1
Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 18 Sex: Male Group: 8 Dose level: 250.000 (mg/kg)
Day of death: 14 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments
THYROID	EDEMA/ ,AROUND THYROID - PP	follicular cell hypertrophy/hyperplasia, Marked. follicular lumen size (decreasing colloid area)1, Moderate.

Study aprf1
Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 86 Sex: Female Group: 1 Dose level: 0.0000 (mg/kg)
Day of death: 14 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments
THYROID	No gross observed on tissue.	follicular lumen size (decreasing colloid area)1, Slight.
GEN CONDITION . . .	GOOD/ ,NGL - PP	

Study aprf1
Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 68 Sex: Female Group: 1 Dose level: 0.0000 (mg/kg)
Day of death: 14 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments
THYROID	No gross observed on tissue.	follicular cell hypertrophy/hyperplasia, Mild. follicular lumen size (decreasing colloid area)1, Slight.
GEN CONDITION . . .	GOOD/ ,NGL - PP	

Study aprf1

Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 100 Sex: Female Group: 1 Dose level: 0.0000 (mg/kg)

Day of death: 15 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments

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GEN CONDITION . . . GOOD/ ,NGL-JWN

The following tissues are examined/unremarkable microscopically: THYROID

Study aprf1
Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 90 Sex: Female Group: 1 Dose level: 0.0000 (mg/kg)
Day of death: 15 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments
THYROID	No gross observed on tissue.	follicular lumen size (decreasing colloid area)1, Slight.
GEN CONDITION . . .	GOOD/ ,ngl-jwn	

Study aprf1

Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 71 Sex: Female Group: 1 Dose level: 0.0000 (mg/kg)

Day of death: 14 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments
THYROID	No gross observed on tissue.	follicular cell hypertrophy/hyperplasia, Mild. follicular lumen size (decreasing colloid area)1, Slight.
GEN CONDITION . . .	GOOD/ ,NGL - PP	

Study aprf1

Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 95 Sex: Female Group: 1 Dose level: 0.0000 (mg/kg)

Day of death: 15 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments

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GEN CONDITION . . . GOOD/ ,NGL-JWN

The following tissues are examined/unremarkable THYROID
microscopically:

Study aprf1

Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 73 Sex: Female Group: 2 Dose level: 1.2500 (mg/kg)

Day of death: 15 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments
THYROID	No gross observed on tissue.	follicular lumen size (decreasing colloid area)1, Slight.
GEN CONDITION . . .	GOOD/ ,NGL-JWN	

Study aprf1

Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 58 Sex: Female Group: 2 Dose level: 1.2500 (mg/kg)

Day of death: 14 Study/dosing pha

Tissue	Gross observations / Comments	Microscopic observations / Comments
THYROID	No gross observed on tissue.	follicular lumen size (decreasing colloid area)1, Slight.
GEN CONDITION . . .	GOOD/ ,NGL - PP	

Study aprf1

Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 67 Sex: Female Group: 2 Dose level: 1.2500 (mg/kg)

Day of death: 15 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments
THYROID	No gross observed on tissue.	follicular cell hypertrophy/hyperplasia, Mild.
GEN CONDITION . . .	GOOD/ ,ngl-jwn	

Study aprf1
Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 51 Sex: Female Group: 2 Dose level: 1.2500 (mg/kg)
Day of death: 14 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments

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GEN CONDITION . . . GOOD/ ,NGL - PP

The following tissues are examined/unremarkable microscopically: THYROID

Study aprf1
Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 55 Sex: Female Group: 2 Dose level: 1.2500 (mg/kg)
Day of death: 14 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments
THYROID	EDEMA/ ,SLIGHT SWELLING BETWEEN THYROID AND TRACHEA - PP	Tissue is missing. / thyroid lost in processing

Study aprf1

Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 84 Sex: Female Group: 2 Dose level: 1.2500 (mg/kg)

Day of death: 15 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments
GEN CONDITION . . .	GOOD/ ,NGL-JWN	

The following tissues are examined/unremarkable microscopically: THYROID

Study aprf1
Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 63 Sex: Female Group: 3 Dose level: 5.0000 (mg/kg)
Day of death: 14 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments
THYROID	No gross observed on tissue.	follicular cell hypertrophy/hyperplasia, Mild. follicular lumen size (decreasing colloid area)1, Slight.
GEN CONDITION . . .	GOOD/ ,NGL - PP	

Study aprf1

Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 69 Sex: Female Group: 3 Dose level: 5.0000 (mg/kg)

Day of death: 15 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments
THYROID	No gross observed on tissue.	follicular cell hypertrophy/hyperplasia, Mild. follicular lumen size (decreasing colloid area)1, Slight.

GEN CONDITION . . . GOOD/ ,ngl-jwn

Study aprf1

Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 91 Sex: Female Group: 3 Dose level: 5.0000 (mg/kg)

Day of death: 15 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments
THYROID	No gross observed on tissue.	follicular cell hypertrophy/hyperplasia, Mild. follicular lumen size (decreasing colloid area)1, Slight.
GEN CONDITION	GOOD/ ,ngl-jwn	

Study aprf1
Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 88 Sex: Female Group: 3 Dose level: 5.0000 (mg/kg)
Day of death: 15 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments
THYROID	No gross observed on tissue.	follicular cell hypertrophy/hyperplasia, Mild. follicular lumen size (decreasing colloid area)1, Slight.
GEN CONDITION . . .	GOOD/ ,ngl-jwn	

Study aprf1
Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 56 Sex: Female Group: 3 Dose level: 5.0000 (mg/kg)
Day of death: 14 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments
THYROID	EDEMA/ ,SLIGHT AROUND THYROIDS - PP	follicular cell hypertrophy/hyperplasia, Mild. follicular lumen size (decreasing colloid area)1, Slight.

Study aprf1
Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 53 Sex: Female Group: 3 Dose level: 5.0000 (mg/kg)
Day of death: 14 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments
THYROID	No gross observed on tissue.	follicular lumen size (decreasing colloid area)1, Slight.
GEN CONDITION . . .	GOOD/ ,NGL - PP	

Study aprf1
Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 99 Sex: Female Group: 4 Dose level: 12.5000 (mg/kg)
Day of death: 15 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments
THYROID	No gross observed on tissue.	follicular cell hypertrophy/hyperplasia, Mild. follicular lumen size (decreasing colloid area)1, Slight.

GEN CONDITION . . . GOOD/ ,ngl-jwn

Study aprf1
Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 77 Sex: Female Group: 4 Dose level: 12.5000 (mg/kg)
Day of death: 15 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments

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GEN CONDITION . . . GOOD/ ,ngl-jwn

The following tissues are examined/unremarkable THYROID
microscopically:

Study aprf1
Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 66 Sex: Female Group: 4 Dose level: 12.5000 (mg/kg)
Day of death: 14 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments
THYROID	No gross observed on tissue.	follicular cell hypertrophy/hyperplasia, Mild. follicular lumen size (decreasing colloid area)1, Slight.
GEN CONDITION . . .	GOOD/ ,NGL - PP	

Study aprf1

Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 70 Sex: Female Group: 4 Dose level: 12.5000 (mg/kg)

Day of death: 14 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments
THYROID	No gross observed on tissue.	follicular lumen size (decreasing colloid area)1, Slight.
GEN CONDITION . . .	GOOD/ ,NGL - PP	

Study aprf1
Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 92 Sex: Female Group: 4 Dose level: 12.5000 (mg/kg)
Day of death: [illegible] Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments
THYROID	No gross observed on tissue.	follicular cell hypertrophy/hyperplasia, Mild. follicular lumen size (decreasing colloid area)1, Slight.
GEN CONDITION . . .	GOOD/ ,NGL-JWN	

Study aprf1
Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 60 Sex: Female Group: 4 Dose level: 12.5000 (mg/kg)
Day of death: 14 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments
THYROID	No gross observed on tissue.	follicular cell hypertrophy/hyperplasia, Mild. follicular lumen size (decreasing colloid area)1, Slight.
GEN CONDITION . . .	GOOD/ ,NGL - PP	

Study aprf1

Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 87 Sex: Female Group: 5 Dose level: 25.0000 (mg/kg)

Day of death: 15 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments
THYROID	No gross observed on tissue.	follicular cell hypertrophy/hyperplasia, Marked. follicular lumen size (decreasing colloid area)1, Moderate.
GEN CONDITION . . .	GOOD/ ,ngl-jwn	

Study aprf1

Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 80 Sex: Female Group: 5 Dose level: 25.0000 (mg/kg)

Day of death: 15 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments
THYROID	No gross observed on tissue.	follicular cell hypertrophy/hyperplasia, Mild. follicular lumen size (decreasing colloid area)1; Slight. / ultimobranchial cyst
GEN CONDITION . . .	GOOD/ ,ngl-jwn	

Study aprf1

Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 59 Sex: Female Group: 5 Dose level: 25.0000 (mg/kg)

Day of death: 14 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments
THYROID	No gross observed on tissue.	follicular cell hypertrophy/hyperplasia, Marked. follicular lumen size (decreasing colloid area)1, Slight. / ultimobranchial cyst
PARATHYROID	ENLARGED/ ,LEFT APPEARS SLIGHTLY ENLARGED - PP	

Study aprf1
Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 94 Sex: Female Group: 5 Dose level: 25.0000 (mg/kg)
Day of death: 15 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments
THYROID	No gross observed on tissue.	follicular cell hypertrophy/hyperplasia, Mild. follicular lumen size (decreasing colloid area)1, Slight.
GEN CONDITION . . .	GOOD/ ,ngl-jwn	

Study aprf1

Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 76 Sex: Female Group: 5 Dose level: 25.0000 (mg/kg)

Day of death: 14 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments
THYROID	No gross observed on tissue.	follicular cell hypertrophy/hyperplasia, Mild. follicular lumen size (decreasing colloid area)1, Moderate.
GEN CONDITION . . .	GOOD/ ,NGL - PP	

Study aprf1
Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 64 Sex: Female Group: 5 Dose level: 25.0000 (mg/kg)
Day of death: 14 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments
THYROID	EDEMA/ ,SLIGHT AROUND THYROIDS - PP	follicular cell hypertrophy/hyperplasia, Mild. follicular lumen size (decreasing colloid area)1, Slight.

Study aprf1

Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 96 Sex: Female Group: 6 Dose level: 50.0000 (mg/kg)

Day of death: 15 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments
THYROID	No gross observed on tissue.	follicular cell hypertrophy/hyperplasia, Marked. follicular lumen size (decreasing colloid area)1, Moderate.
GEN CONDITION . . .	GOOD/ ,ngl-jwn	

Study aprf1
Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 62 Sex: Female Group: 6 Dose level: 50.0000 (mg/kg)
Day of death: 15 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments
THYROID	No gross observed on tissue.	follicular cell hypertrophy/hyperplasia, Mild. follicular lumen size (decreasing colloid area)1, Slight.
GEN CONDITION . . .	GOOD/ ,ngl-jwn	

Study aprf1

Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 61 Sex: Female Group: 6 Dose level: 50.0000 (mg/kg)
Day of death: 14 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments
THYROID	No gross observed on tissue.	follicular cell hypertrophy/hyperplasia, Marked. follicular lumen size (decreasing colloid area)1, Moderate.
GEN CONDITION . . .	GOOD/ ,NGL - PP	

Study aprf1

Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 85 Sex: Female Group: 6 Dose level: 50.0000 (mg/kg)

Day of death: 15 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments
THYROID	No gross observed on tissue.	follicular cell hypertrophy/hyperplasia, Mild. follicular lumen size (decreasing colloid area)1, Slight.
GEN CONDITION . . .	GOOD/ ,ngl-jwn	

Study aprf1

Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 52 Sex: Female Group: 6 Dose level: 50.0000 (mg/kg)

Day of death: 14 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments
THYROID	EDEMA/ ,SLIGHTLYLAROUND THYROIDS - PP	follicular cell hypertrophy/hyperplasia, Mild. follicular lumen size (decreasing colloid area)1, Slight.

Study aprf1

Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 57 Sex: Female Group: 6 Dose level: 50.0000 (mg/kg)

Day of death: 14 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments
THYROID	No gross observed on tissue.	follicular cell hypertrophy/hyperplasia, Mild. follicular lumen size (decreasing colloid area)1, Slight.
GEN CONDITION . . .	GOOD/ ,NGL - PP	

Study aprf1

Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 93 Sex: Female Group: 7 Dose level: 125.000 (mg/kg)

Day of death: 15 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments
THYROID	No gross observed on tissue.	follicular cell hypertrophy/hyperplasia, Mild. follicular lumen size (decreasing colloid area)1, Severe.
GEN CONDITION . . .	GOOD/ ,ngl-jwn	

Study aprf1

Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 82 Sex: Female Group: 7 Dose level: 125.000 (mg/kg)

Day of death: 15 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments
THYROID	No gross observed on tissue.	follicular cell hypertrophy/hyperplasia, Marked. follicular lumen size (decreasing colloid area)1, Moderate.
GEN CONDITION . . .	GOOD/ ,ngl-jwn	

Study aprf1

Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 81 Sex: Female Group: 7 Dose level: 125.000 (mg/kg)

Day of death: 15 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments
THYROID	No gross observed on tissue.	follicular cell hypertrophy/hyperplasia, Marked. follicular lumen size (decreasing colloid area)1, Moderate.
GEN CONDITION . . .	GOOD/ ,ngl-jwn	

Study aprf1
Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 78 Sex: Female Group: 7 Dose level: 125.000 (mg/kg)
Day of death: 14 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments
THYROID	No gross observed on tissue.	follicular cell hypertrophy/hyperplasia, Marked. follicular lumen size (decreasing colloid area)1, Moderate.
GEN CONDITION . . .	GOOD/ ,NGL - PP	

Study aprf1

Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 65 Sex: Female Group: 7 Dose level: 125.000 (mg/kg)

Day of death: 14 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments
THYROID	EDEMA/ ,SLIGHT AROUND THYROIDS - PP	follicular cell hypertrophy/hyperplasia, Mild. follicular lumen size (decreasing colloid area)1, Slight.

Study aprf1
Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 79 Sex: Female Group: 7 Dose level: 125.000 (mg/kg)
Day of death: 14 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments
THYROID	No gross observed on tissue.	follicular cell hypertrophy/hyperplasia, Marked. follicular lumen size (decreasing colloid area)1, Moderate.
GEN CONDITION . . .	GOOD/ ,NGL - PP	

Study aprf1
Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 74 Sex: Female Group: 8 Dose level: 250.000 (mg/kg)
Day of death: 14 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments
THYROID	No gross observed on tissue.	follicular cell hypertrophy/hyperplasia, Marked. follicular lumen size (decreasing colloid area)1, Moderate.
GEN CONDITION . . .	GOOD/ ,NGL - PP	

Study aprf1
Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 83 Sex: Female Group: 8 Dose level: 250.000 (mg/kg)
Day of death: 15 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments
THYROID	No gross observed on tissue.	follicular cell hypertrophy/hyperplasia, Marked. follicular lumen size (decreasing colloid area)1, Severe.
GEN CONDITION	GOOD/ ,NGL-JWN	

Study aprf1

Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 75 Sex: Female Group: 8 Dose level: 250.000 (mg/kg)

Day of death: 15 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments
THYROID	No gross observed on tissue.	follicular cell hypertrophy/hyperplasia, Marked. follicular lumen size (decreasing colloid area)1, Severe.
GEN CONDITION . . .	GOOD/ ,ngl-jwn	

Study aprf1
Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 89 Sex: Female Group: 8 Dose level: 250.000 (mg/kg)
Day of death: 15 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments
THYROID	No gross observed on tissue.	follicular cell hypertrophy/hyperplasia, Marked. follicular lumen size (decreasing colloid area)1, Moderate.
GEN CONDITION . . .	GOOD/ ,ngl-jwn	

Study aprf1

Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 54 Sex: Female Group: 8 Dose level: 250.000 (mg/kg)

Day of death: 14 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments
THYROID	EDEMA/ ,SLIGHT AROUND THYROID - PP	follicular cell hypertrophy/hyperplasia, Marked. follicular lumen size (decreasing colloid area)1, Severe.

Study aprf1

Individual Animal Report of Gross and Microscopic Diagnoses

Animal: 72 Sex: Female Group: 8 Dose level: 250.000 (mg/kg)

Day of death: 14 Study/dosing phase

Tissue	Gross observations / Comments	Microscopic observations / Comments
THYROID	No gross observed on tissue.	follicular cell hypertrophy/hyperplasia, Marked. follicular lumen size (decreasing colloid area)1, Moderate.
GEN CONDITION . . .	GOOD/ ,NGL - PP	